600-1-081CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Steinman et al. EXAMINER: Schwadron, Ronald B.

SERIAL NO.: 09/586,704 ART UNIT: 1644

FILED: June 5, 2000

FOR: IDENTIFICATION OF DEC, A RECEPTOR WITH C-TYPE LECTIN DOMAINS, NUCLEIC ACIDS ENCODING DEC, AND USES THEREOF

DECLARATION UNDER 37 C.F.R. 1.132

COMMISSIONER FOR PATENTS
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SIR:

I, MICHEL NUSSENZWEIG, hereby declare and state that:

1. I am a Howard Hughes Investigator, Sherman Fairchild Professor and Senior Physician at Rockefeller University having received my Ph.D. degree from the Rockefeller University in 1981 and my M.D. degree from New York University in 1982. I received postdoctoral medical and scientific training at Harvard University. My full curriculum vitae is attached hereto as Exhibit A.

2. My principal area of research is in Immunology and among other positions I serve as reviewer in numerous funding agencies of many countries, including the National Institute of Health, March of Dimes, Dana Foundation. I also have served as reviewer for numerous scientific journals, and I am the Editor of the Journal of Experimental Medicine and the Journal of Immunologic Methods.

3. In the course of my activities, I have been listed as inventor on several patent applications, including the one noted above entitled IDENTIFICATION OF DEC, A RECEPTOR WITH C-TYPE LECTIN DOMAINS, NUCLEIC ACIDS ENCODING DEC, AND USES THEREOF, having U.S. Serial Number 09/586,704, which is a

continuation of U.S. application Serial Number 08/381,528, filed on January 31, 1995, now abandoned.

4. I have reviewed the disclosure of the present application, with particular emphasis on the subject matter of the present application and in particular, how the pending claims differ from the art cited by the Examiner.

5. The present application claims a vaccine for inducing an immune response comprising an antigen from a pathogen conjugated to a Dendritic and Epithelial Cell-205 (DEC-205) ligand, wherein the DEC-205 ligand is an anti-human DEC-205 antibody or an anti-murine DEC-205 antibody reactive with a human DEC-205 protein and an immune stimulator.

6. Based on the subject matter of the present application, it is my opinion that there was no teaching in the art that DEC-205 was an endocytic receptor which functioned to deliver an antigen to an antigen-processing compartment in a cell, prior to the time of our invention. Nemazee discloses cell surface receptors, but does not disclose DEC-205. Many surface receptors do not deliver antigens to processing compartments. For example, antigens bound to macrophage mannose receptor on dendritic cells, which is a close relative of DEC-205, are internalized but not processed and presented (Mahnke, K., Guo. M., Lee, S., Sepulveda, H., Swain, S.L., Nussenzweig, M.C. & Steinman, R.M.; (2000), The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via MHC II+, lysosomal compartments, *J. of Cell Biology* 151:673-683). There are no known sequences that act as targeting sequences for antigen processing compartments, and furthermore, the sequence of DEC-205 was not known in any case. Thus, it would not be possible for one skilled in the art to know that DEC-205 would function as an endocytic receptor for antigen delivery to processing compartments, thus making this mechanism potentially useful in the area of vaccine development.

7. Furthermore, the disclosure in Nemazee is based on David Parker s original finding published in the *Journal of Experimental Medicine* (Tony HP., Parker DC, (1985), Major histocompatibility complex-restricted, polyclonal B cell responses resulting from helper T cell recognition of antiimmunoglobulin presented by small B lymphocytes, *Journal of*

Experimental Medicine, 161(1): 223-41), which demonstrates that antibodies to B cell surface immunoglobulin could be processed and presented *in vitro*. One skilled in the art would know that this technique has never been used to immunize or tolerize in man, probably because B cells simply function as initiators of immune responses *in vivo* although they can act as antigen presenting cells secondarily. Thus, one skilled in the art would not deduce that antigen targeting with antibodies would work *in vivo*.

8. Thus, in addressing the Examiner s position that the Kraal antibody binds DEC, I can state and attest that the opposite is, in fact, true as relates to the inability of the Kraal antibody to bind human DEC-205. My laboratory has cloned and expressed human DEC-205 (Guo, M., Gong, S., Maric, S., Misulovin, Z., Pack, M., Mahnke, K., Nussenzweig, M.C. & Steinman, R.; (2000), A monoclonal antibody to the DEC-205 endocytosis receptor on human dendritic cells, *Human Immunology* 61:729-738) and we have tested our antibodies, as well as the NLDC-145 antibody, for reactivity to the human DEC-205 protein, and we have obtained quite different results. **The Kraal NLDC-145 antibody does not react with human DEC-205.** We noted this in our current patent application in lines 15-19 on page 3 of the specification, which states that **human DEC-205 is characterized by not reacting with monoclonal antibody NLDC-145.** Further support in our pending application can be found in lines 10-13, on page 45, where we state that an advantage of our present invention is that the antibodies described in the application can be used to target molecules to **human** dendritic cells. As we noted in the application, It is recognized that this is a significant advantage, since the prior art antibody of Kraal et al. failed to recognize human DEC. . Since the reactivity of our antibodies with human DEC-205 protein is part of our description and claims, I believe that this differentiates our antibodies over the antibody described by Kraal.

9. Furthermore, it was the work done in my laboratory that helped to identify human DEC-205 and its significance as an endocytic receptor. Further cloning and expression of the protein then pointed to the differences in the reactivity of the Kraal antibody compared to our own antibodies. Thus, it would not have been obvious to one skilled in the art to practice the use of our antibodies reactive to human DEC-205 protein for targeting antigens to human DEC-205 protein, or to use it for vaccines for eliciting an immune response, since neither the antibodies developed by my laboratory nor the

existence of human DEC-205 was known prior to our own work. Thus, the information in the field was insufficient to enable the skilled person to combine the teachings of Kraal with the teachings of Nemazee and to result in the use of our antibodies that react with human DEC-205 to produce the desired immunological response.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18 of the U.S. Code, Section 1001, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: 9/19/03

Michel Nussenzweig, M.D., Ph.D.

EXHIBIT A

CURRICULUM VITAE

Name: Michel C. Nussenzweig

Date of Birth: February 10, 1955

Education:

1975	B.A. - New York University College of Arts and Sciences
1981	Ph.D. - The Rockefeller University
1982	M.D. - New York University School of Medicine

Clinical Training:

1982-1985	Intern & Resident, Internal Medicine Massachusetts General Hospital
1984-1985	Clinical Fellow, Infectious Diseases Massachusetts General Hospital

Postdoctoral Training:

1986-1989	Harvard Medical School, Department of Genetics

Professional Appointments

1990-1996	Assistant & Associate Professor, The Rockefeller University
1990-1999	Assistant & Associate Investigator, Howard Hughes Medical Institute
1996-present	Professor & Senior Physician, The Rockefeller University
1999-present	Investigator, Howard Hughes Medical Institute
2000-present	Sherman Fairchild Professor of Immunology, The Rockefeller Univ.

Honors & Awards

Summa Cum Laude, New York University College of Arts and Sciences - 1975; Phi Beta Kappa, New York University College of Arts and Sciences - 1975; Alpha Omega Alpha, New York University Medical School - 1982; Bertram M. Gresner Memorial Research Award, New York University School of Medicine – 1982; Elected Member American Society of Clinical Investigators - 1997, Solomon A. Berson Award for Basic Science - 2002

Teaching:

Immunology, Course Organizer

Institutional:

Chair, Transgenic Facility Coordinating Committee
Chair, Animal Care and Use Committee

Chair, Hospital Seminar Committee
Member, Immunology Search Committee
Member, Institutional Review Board for Biohazards, Radioisotopes, Toxic Chemicals, and Carcinogens
Member Hospital GCRC Scientific Advisory Committee
Elected Senior Faculty Representative Academic Council
Member, Virology Search Committee

National
Arthritis Foundation Molecular Immunology study section 1993-1996
NIH Immunobiology Study Section Ad Hoc reviewer 1998, and 1999
NIH ALY Study Section Ad Hoc Reviewer, 1999
NIH NIAID Council Ad Hoc 1998
Organizer Keystone Symposium on Dendritic Cells 1998
Organizer Keystone Symposium on B Cells 1999
March of Dimes Review Committee 1999-
External Reviewer LMGD NICHD 2000
Damon Runyon Cancer Research Fund Review Committee 2000-2002
American Association of Immunologists Program Committee 2000-
NIH ALY Study Section Member 2001-
Organizer Keystone Symposium on B Cell Biology 2003

Editorial:

1996-Present	Editor, The Journal of Experimental Medicine
1999-Present	Editor, The Journal of Immunological Methods
2000-Present	Transmitting Editor, International Immunology
2002-Present	Advisory Editor, Nature Reviews Immunology

Consultant:
Abgenix, Fremont, CA
Zycos, Lexington MA

Professional Memberships:
American Association of Immunologists
American Medical Association
The New York Academy of Sciences
Kunkel Society
Harvey Society

Publications:

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3. **Nussenzweig, M.C.** & Steinman, R.M. Contribution of dendritic cells to stimulation of the syngeneic mixed leukocyte reaction. *J. Exp. Med.* 151:1196-1212. (1980)

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56. Yu, W., Misulovin, Z., Suh, H., Hardy, R.R., Jankovic, M., Yannoutsos, N & **Nussenzweig, M.C.** Coordinate regulation of RAG1 and RAG2 by cell type-specific DNA elements 5' of RAG2. *Science* 285:1080-1084 (1999)

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